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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,674	07/13/2001	Christoph Reinhard	PP-01700.002 / 200130.521	4819
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Chiron Corporation Intellectual Property R338 P.O. Box 8097 Emeryville, CA 94662-8097			LACOURCIERE, KAREN A	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/905,674

Applicant(s)

REINHARD ET AL.

Examiner

Karen A. Lacourciere

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24 and 35 is/are allowed.
- 6) ☒ Claim(s) 23, 25-34 and 36-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The rejection of record of claims 25-35 under 35 U.S.C. 112, second paragraph, set forth in the prior Office action, mailed 02-25-2003, is withdrawn in response to Applicant's amendments filed 07-29-2003, however new ground(s) of rejection under 35 USC 112 second paragraph are set forth herein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 has been amended such that the claim encompasses 2 separate sentences, therefore, it is unclear is part d of the claim is meant to be included in the claim or not. Further, claim 23 has been amended such that there is no conjunction between the recited portions of the claim (a, b, c and d) and therefore, it is unclear if the parts of the claim are meant to be in the alternative or not, or if there are further, unrecited, members of the group. Claim 34 is indefinite for the same reasons due to dependence on claim 23.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25-34 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising SEQ ID NO:1, does not reasonably provide enablement for generally any nucleic acid encoding SEQ ID NO:2 or fragments thereof, a polypeptide that is 90% identical to SEQ ID NO:2, the complement of said sequences, or polynucleotides encoding a polypeptide with up to 50 substitutions in said sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23, 25-34 and 36-38 are drawn to polynucleotides encoding amino acids 1-270 of SEQ ID NO:2, polynucleotides encoding amino acids 2-270 of SEQ ID NO:2, the complement of polynucleotides encoding amino acids 1-270 or 2-270 of SEQ ID NO:2, or a polynucleotide with at least 90% identity to any of these sequences. The claims are further drawn to any of these polynucleotides, wherein there is at least one conservative substitution in the encoded amino acid and as many as 50 conservative substitutions in the encoded amino acid. The claims are further drawn to polynucleotides encoding a polypeptide comprising a an amino acid sequence of SEQ ID NO:13 or 14, which are fragments of SEQ ID NO:2.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification, as filed, provides one example of a polynucleotide, SEQ ID NO:1, which encodes a polypeptide of SEQ ID NO:2. The specification discloses that SEQ ID NO:1 is expressed at a level 9 times higher in cancer prostate cells versus normal prostate cells. The differential expression of SEQ ID NO:1 in prostate cancer cells relative to normal prostate cells would provide a use for SEQ ID NO:1 as a marker for abnormal prostate cells. This use would not correlate generally with any polynucleotide encoding a polypeptide of SEQ ID NO:2, or variants of those sequences, because, given the degeneracy of the code, other polynucleotides would have a sequence that is highly variant from SEQ ID NO:1 and the specification has not demonstrated that any other sequence exists in cells and is upregulated in cancer cells relative to normal cells and, therefore, would not be useful as a marker for prostate cancer. Any other polynucleotide encoding SEQ ID NO:2 would have use only as a tool for expressing SEQ ID NO:2, however, the specification has not provided a practical, specific and substantial use for a polypeptide of SEQ ID NO:2.

The specification demonstrates that antisense targeted to SEQ ID NO:1 inhibits the level of SEQ ID NO:1 in SW260 cells. One antisense molecule was administered to SW260 cells in a 4-day experiment and cell growth appears lower in antisense cells than in untreated cells, however, a control oligonucleotide also significantly inhibited cell growth. As presented, the antisense results appear to be raw numbers, without any

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normalization to account for factors including, for example, differences in cell number at day one or inhibition of cell growth due to general toxicity of the antisense molecule, rather than a specific effect of inhibiting proliferation by decreasing levels of SEQ ID NO:1. The specification does not provide any interpretation of these results and the significance of these results is unclear. It is unclear that inhibition of expression of SEQ ID NO:1 or inhibition of the production of a polypeptide of SEQ ID NO:2 would correlate with an inhibition of cell proliferation.

The specification does not demonstrate the a polypeptide of SEQ ID NO:2 is actually expressed in cells, nor does it demonstrate that levels of a polypeptide of SEQ ID NO:2 correlate with a cancer state in a cells. The specification does not assess whether their antisense molecule decreases levels of a polypeptide of SEQ ID NO:2 in cells. The specification sets forth SEQ ID NO:2 as a member of the tetraspan protein superfamily and a member of a specific family within the superfamily known as NET proteins ("new EST tetraspan"). The specification sets forth SEQ ID NO:2 as a protein named TSPAN-7, based on sequence similarity with a protein named NET-4 or TSPAN-5, disclosed by Serru et al. (reference AO on PTO form 1449, filed October 15, 2001). Serru et al. have assigned an identity to their NET proteins as tetraspan proteins based on sequence similarity with tetraspan proteins in the database, but have not functionally characterized these proteins, including NET-4/TSPAN-5. The tetraspan protein family is characterized by certain structural characteristics, including 4 transmembrane domains and conserved residues (see Serru et al. and figure 1 of the instant specification, for example), however, the specification has not disclosed these conserved features in

SEQ ID NO:2, for example, although the specification points to two extracellular domains (SEQ ID NO:13 and 14) in SEQ ID NO:2, it is not readily apparent whether SEQ ID NO:2 possesses any of the other structural characteristics of tetraspan proteins because the specification does not point out conserved residues or transmembrane domains and the vague nature of the consensus makes it hard to determine by looking at the amino acid sequence.

Further, although Applicant relies on sequence similarity between SEQ ID NO:2 and tetraspan proteins known in the art, absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited

specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981 (1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]; Attwood et al. (Science, Vol. 290, No. 5491, pages 471-473, 2000); and Kyripdes et al. (Molecular Microbiology, Vol. 32, pages 886-887, 1999). In the instant case, the uncertainty of function based on sequence similarity is multiplied, since the function of SEQ ID NO:2 was based on sequence similarity with NET-4, which has not been characterized and whose function was assigned based on sequence similarity with another protein.

Additionally, Serru et al. discusses tetraspan proteins and states that the expression levels of known members of the family (eg. CD9, CD63 and CD82) are inversely correlated with metastatic potential of several cancers, which seems to be an opposite effect to that observed with levels of SEQ ID NO:1 in the instant specification. As such, SEQ ID NO:1, and a protein encoded by such, SEQ ID NO:2, would seem not to exhibit the functional characteristics of tetraspan proteins, either.

The specification sets forth the use of polynucleotides encoding SEQ ID NO:2 as a means to express and isolate a polypeptide of SEQ ID NO:2. The specification sets forth uses of this polypeptide to make antibodies and other antagonists that inhibit the polypeptide and for use in screening assays to determine inhibitors of the polypeptide, which in turn are contemplated for use in treatment methods for cancer. These uses are not considered to be credible, because the specification has not even demonstrated that SEQ ID NO:2 is expressed in cells, or provided any characterization

of the protein such that the skilled artisan would recognize that SEQ ID NO:2 has a correlation with any disease, including cancer. A polynucleotide that is useful only to produce a protein, which does not have a use, is not considered to have a real world, specific and substantial utility. Therefore, the specification has not taught the skilled artisan how to use any polynucleotide encoding SEQ ID NO:2, besides SEQ ID NO:1, with out undue trial an error experimentation. This experimentation would include the characterization of a polypeptide of SEQ ID NO:2, for example, as to whether it is actually expressed and whether its expression correlates with cancer, or if the protein has a function, and the determination if there is a use for this polypeptide, or a polynucleotide encoding such, other than SEQ ID NO:1, and what that use is. This would need to be determined de novo, through undue trial and error experimentation, beyond the teachings of the specification.

Response to Arguments

Applicant's arguments filed 07-29-2003 have been fully considered but they are not persuasive. In response to the rejection of record of claims 23 and 25-38 under 35 U.S.C. 112, first paragraph, regarding a lack of an enabled use for the full scope claimed, Applicant argues that the level of experimentation to practice the claimed invention does not rise to the level of undue experimentation. Applicant addresses each of the *Wands* factors with regard to how the skilled artisan is enabled for finding polynucleotides that fall within the scope of the claimed polynucleotides. Applicant argues that probing for the claimed polynucleotides is routine and requires only transfection of cells, which is also routine and then determining if an antibody to

TSPAN-7 binds to the polypeptide. Applicant points to examples and guidance in the specification for making the claimed polynucleotides. Applicant argues the nature of the invention is such that the skilled artisan could make the claimed polynucleotides and all of the methods for making such were well known and that the skilled artisan would be highly skilled.

These arguments have been fully considered, but have not been found to be persuasive. Although obtaining polynucleotides that fall within the scope of the claimed invention may have been routine, the specification has not fulfilled the requirement to enable the skilled artisan to use the full scope of the claimed polynucleotides. Applicant's arguments do not address the *Wands* factors with respect to the ability to use the claimed polynucleotides over the full scope claimed, as the rejection of record is directed. As discussed in the rejection of record, the one enabled use for the polynucleotides claimed is for that as a probe, based on the differential level of expression of SEQ ID NO:1. The differential expression of SEQ ID NO:1 in prostate cancer cells relative to normal prostate cells would provide a use for SEQ ID NO:1 as a marker for abnormal prostate cells. This use would not correlate generally with any polynucleotide encoding a polypeptide of SEQ ID NO:2, or variants of those sequences, because, given the degeneracy of the code, other polynucleotides would have a sequence that is highly variant from SEQ ID NO:1 and the specification has not demonstrated that any other sequence exists in cells and is upregulated in cancer cells relative to normal cells and, therefore, would not be useful as a marker for prostate cancer. Any other polynucleotide encoding SEQ ID NO:2 would have use only as a tool

for expressing SEQ ID NO:2, however, the specification has not provided a practical, specific and substantial use for a polypeptide of SEQ ID NO:2. Applicant does not argue the enablement of a use for these variant sequences encompassed in the claims and do not appear to address the rejection based on a lack of an enabled use for the scope of the claim and, therefore, the rejection has been maintained for the reasons of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 23, 25-34, 37 and 38 are maintained as rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al. (WO 99/58660, cited on PTO form 1449, filed October 15, 2001).

Ruben et al. disclose an isolated polynucleotide that encodes a polypeptide which is 99.63% identical to SEQ ID NO:2, with one conservative mismatch at amino acid residue 27 (see, for example, SEQ ID NO: 20 of Ruben et al.) This polynucleotide encodes a polypeptide comprising SEQ ID NO:13 and 14.

Therefore, Ruben et al. anticipates claims 23, 25-34, 37 and 38.

Response to Arguments

In response to the rejection of record of Claims 23, 25-35, 37 and 38 under 35 U.S.C. 102(a) as being anticipated by Ruben et al. (WO 99/58660, cited on PTO form 1449, filed October 15, 2001) applicant argues that Ruben et al. disclose a polynucleotide encoding a polypeptide with only 88% identity to SEQ ID NO:2 when calculations are made taking into account the portions of the polypeptide of Ruben et al. that do not appear in the claimed Tetraspan-7 protein. This is not found to be persuasive because the language of the claim is comprising and, therefore, open and would encompass proteins that include additional sequence, as disclosed by Ruben et al. Ruben et al. discloses a polynucleotide encoding a polypeptide that comprises a sequence 99.63% identical to SEQ ID NO:2 and, therefore, anticipates the claimed invention.

Conclusion

Claims 24 and 35 are Allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
October 20, 2003


KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER